DETAILED ACTION

Claims 1–10 and 89–96 are pending.

Applicant's election with traverse of non-atmospheric ratios of atmospheric gases in the reply filed on 07/31/2007 is acknowledged. The traversal is on the ground(s) that the various species could all be searched together without undue burden. This is not found persuasive because the species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record. Therefore, the various species could not all be searched together without undue burden.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 09/120,264, 09/087,210 and 08/864,357, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The claims are directed to or encompass a method of treat comprising improving and/or normalizing lung function in a patient in need of such treatment, a method of treat comprising improving and/or normalizing pulmonary compliance resulting from exposure to one or more substances selected from the group consisting of non-atmospheric gases, non-atmospheric ratios of atmospheric gases, inhaled chemicals, pollutant, irritants, inhaled pollens, allergens, particulate matter, and an airborne infectious agent, wherein said nonatmospheric ratios of atmospheric gases comprises elevated oxygen delivery in a patient in need of such treatment, and a method of treatment comprising improving blood oxygenation and/or normalizing blood pH in a patient in need of such treatment. The disclosure of the prior-filed applications, Application Nos. 09/120,264, 09/087,210 and 08/864,357, fail to provide adequate support in the manner provided by the first paragraph of 35 U.S.C. 112 for these limitations.

The claims are directed to or encompass a method of treatment comprising administering 10 ng to 25 mg of UG per kg of body weight. The disclosure of the prior-filed applications, Application Nos. 09/120,264, 09/087,210 and 08/864,357, fail to provide adequate support in the manner provided by the first paragraph of 35 U.S.C. 112 for this limitation.

Claim Objections

Claims 2, 4, 6 and 9 are objected to because of the following informalities: "SEQ ID NO 1" should be "SEQ ID NO: 1". Appropriate correction is required.

Claims 1, 8 and 9 are objected to because of the following informalities: "SEQ ID NQ 1" should be "SEQ ID NO: 1". Appropriate correction is required.

Claims 3, 7, 10, 93 and 95 are objected to because of the following informalities: "ofbody" should be "of body". Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 89-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment comprising administering UG comprising the amino acid sequence of SEQ ID NO: 1, does not reasonably provide enablement for a method of treatment comprising administering recombinant human uteroglobin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to or encompass a method of treatment comprising administering recombinant human uteroglobin. The specification defines human uteroglobin as follows:

> Native and recombinant human uteroglobin may be used in the present invention. In a preferred embodiment, however, recombinant human uteroglobin is employed in the methods and compositions of the invention. The recombinant form of uteroglobin preferably has substantially the same amino acid sequence as that of the native human uteroglobin protein. An amino acid sequence having "substantially the same" amino acid sequence as that of the native human protein includes recombinant human uteroglobin having at least 75% identity to the native human protein. In a preferred embodiment, recombinant human uteroglobin has at least 85% identity, and in a most preferred embodiment, recombinant human uteroglobin has at least 98% identity to the native uteroglobin. In a further preferred embodiment, oxidized dimeric recombinant human uteroglobin is used in the methods and compositions of the present invention (with respect to the various forms of uteroglobin, reference is made to U.S. Ser. No. 09/120,264).

Page 12, last full paragraph. Also according to the specification:

> The absence of structural identity among uteroglobin-like proteins makes it impossible to predict whether a protein will possess in vivo therapeutic function in humans based on in vitro or other activity exhibited by a structurally related protein.

Page 3, full paragraph 2. Accordingly, there is a lack of predictability in the art.

There are no working examples of a UG having less than 100% identity to SEQ ID NO: 1 in the claimed method. The examiner is aware working examples are not required. Lack of a working example is, however, a factor to be considered.

The skilled artisan is left to an extensive amount of random, trial and error experimentation, wherein proteins having less than 100% identity to SEQ ID NO: 1 are randomly made and tested for usefulness in the claimed methods.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 89–95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 89–95 are indefinite because they recite the term "recombinant human uteroglobin." The specification defines human uteroglobin as follows:

> Native and recombinant human uteroglobin may be used in the present invention. In a preferred embodiment, however, recombinant human uteroglobin is employed in the methods and compositions of the invention. The recombinant form of uteroglobin preferably has substantially the same amino acid sequence as that of the native human uteroglobin protein. An amino acid sequence having "substantially the same" amino acid sequence as that of the native human protein includes recombinant human uteroglobin having at least 75% identity to the native human protein. In a preferred embodiment, recombinant human uteroglobin has at least 85% identity, and in a most preferred embodiment, recombinant human uteroglobin has at least 98% identity to the native uteroglobin. In a further preferred embodiment, oxidized dimeric recombinant human uteroglobin is used in the methods and compositions of the present invention (with respect to the various forms of uteroglobin, reference is made to U.S. Ser. No. 09/120,264).

Page 12, last full paragraph. Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "recombinant human uteroglobin" an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element. The metes and bounds are not clearly set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1–10 and 89–96 are rejected under 35 U.S.C. 102(b) as being anticipated by Pilon (WO 98/53846) in view of Mantile (J Biol Chem. 1993 Sep 25;268(27):20343-51) and Arkovitz (Journal of Surgical Research, (1997 Feb 1) 67 (2) 193 8).

A 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure;"
(B) Explain the meaning of a term used in the primary reference; or
(C) Show that a characteristic not disclosed in the reference is inherent.

MPEP § 2131.01.

The disclosure of the prior-filed applications, Application Nos. 09/120,264, 09/087,210 and 08/864,357, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for the claims of this application, as discussed above. Accordingly, Pilon is prior art.

The claims are directed to or encompass a method of treat comprising improving and/or normalizing lung function in a patient in need of such treatment, a method of treat comprising improving and/or normalizing pulmonary compliance in a patient in need of such treatment, and a method of treatment comprising improving blood oxygenation and/or normalizing blood pH in a patient in need of such treatment. According to the present specification, patients with RDS are patients in need of improving and/or normalizing lung function and pulmonary compliance and in need of improving blood oxygenation and/or normalizing blood pH (page 6, lines 4-23). The examiner uses applicants' specification as a dictionary for a definition of the term "patient in need of said treatment."

Pilon teaches ARDS and neonatal RDS/BPD are candidates for the treatment by the administration of UG (page 13, lines 5-20; page 18, line 11 through page 19, line 30). UG may be administered either alone or in combination with other active agents typically used in the treatment of ARDS and neonatal RDS (page 20, lines 17-19). In the treatment of neonatal RDS/BPD adult RDS UG may be administered via an intratracheal tube (page 21, lines 15-17). Local intratracheal administration of UG to the lungs requires 0.2 μg/kg to 500 mg/kg. The UG

is usually administered in a single bolus of 20 ng/kg to 500 mg/kg. See page 23, lines 6-13. Either of these ranges overlaps and is overlapped by the claimed range of 10 ng/kg to 25 mg/kg. UG may be administered in combination with lung surfactant (page 23, lines 6-27). UG inhibits hydrolysis of surfactant by PLA_2 and lung surfactant is used to treat neonates with RDS and adults with RDS (ARDS) (page 26, lines 19-21).

Accordingly, Pilon teaches a method of treatment comprising improving and/or normalizing lung function or pulmonary compliance or a method of treatment comprising improving blood oxygenation and/or normalizing blood pH said method comprising administering UG or UG in combination with lung surfactant.

According to Arkovitz, in the pediatric population, oxygen is administered to neonates as part of the treatment of newborn respiratory distress syndrome. Prolonged exposure to oxygen leads to the development of chronic lung disease or death. In premature infants this chronic lung injury is called bronchopulmonary dysplasia (BPD). Infants with BPD have persistent pulmonary dysfunction and frequent hospitalizations and often develop secondary cardiac disease. See page 193, paragraph bridging left and right columns. Hyperoxia has been shown to decrease pulmonary compliance (page 193, right column, last full paragraph).

Accordingly, Pilon teaches a method of treatment comprising improving and/or normalizing pulmonary compliance in a patient in need of said treatment, said method comprising administering an amount of uteroglobin to said patient sufficient to improve and/or normalize pulmonary compliance relative to pulmonary compliance in the absence of said treatment, wherein said patient suffers from reduced pulmonary compliance as a result of a

pulmonary challenge or insult resulting from exposure to elevated oxygen delivery, said method comprising administering UG or UG in combination with lung surfactant.

Pilon's recombinant human UG was obtained by the method of Mantile (J Biol Chem. 1993 Sep 25;268(27):20343-51) (page 24, line 18). According to Mantile, Ala-Ala was added to the NH_2 terminus as a consequence of plasmid construction (page 20348, Table I).

Pilon's UG comprises the amino acid sequence of SEQ ID NO: 1, as indicated in the sequence comparison below (Qy = SEQ ID NO: 1; Db = Pilon's UG):

```
ID   AAW87569 standard; protein; 70 AA.
*
*
*
PN   WO9853846-A1.
*
*
*
  Query Match           100.0%;  Score 351;  DB 2;  Length 70;
  Best Local Similarity  100.0%;  Pred. No. 1e-35;
  Matches   70;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 EICPSFQRVIETLLMDTPSSYEAAMELFSPDQDMREAGAQLKKLVDTLPQKPRESIIKLM 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 EICPSFQRVIETLLMDTPSSYEAAMELFSPDQDMREAGAQLKKLVDTLPQKPRESIIKLM 60

Qy         61 EKIAQSSLCN 70
              ||||||||||
Db         61 EKIAQSSLCN 70.
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Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1–10 and 89–96 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1–10 of U.S. Patent No. 6,225, 281 in view of Mantile (J Biol Chem. 1993 Sep 25;268(27):20343-51).

Claims 1–10 and 89–96 are directed to or encompass a method of treat comprising improving and/or normalizing lung function in a patient in need of such treatment, a method of treat comprising improving and/or normalizing pulmonary compliance in a patient in need of such treatment, and a method of treatment comprising improving blood oxygenation and/or normalizing blood pH in a patient in need of such treatment. According to the present specification, patients with RDS are patients in need of improving and/or normalizing lung function and pulmonary compliance and in need of improving blood oxygenation and/or normalizing blood pH (page 6, lines 4-23). The examiner uses applicants' specification as a dictionary for a definition of the term "patient in need of said treatment."

Claims 1–10 of U.S. Patent No. 6,225, 281 are directed to or encompass a method treatment comprising administering UG in a patient afflicted with or at risk of a fibrotic condition. According to the patent's specification, a patient afflicted with or at risk of a fibrotic condition, is a patient with RDS (column 1, full paragraph 2; column 3, lines 35-50; paragraph bridging columns 3-4). The examiner uses the patent's specification as a dictionary for a definition of a patient afflicted with or at risk of a fibrotic condition.

Therefore, a method of improving and/or normalizing lung function, blood pH or blood oxygenation encompasses or overlaps a method treatment comprising administering UG in a patient afflicted with or at risk of a fibrotic condition because each treatment method encompasses the treatment of same patient population with overlapping doses of the same compound. Inhibiting fibronectin-fibronectin binding would naturally flow from following the teachings of claims of the present application.

According to Mantile, Ala-Ala was added to the NH_2 terminus as a consequence of plasmid construction (page 20348, Table I), which resulted in a higher efficiency of expression (page 20346, paragraph bridging left and right columns).

This is a provisional obviousness-type double patenting rejection.

Claims 1–10 and 89–96 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 193–198 and 200 of copending Application No. 11/189,229 (U. S. Publication No. 20060025348) in view of Mantile (J Biol Chem. 1993 Sep 25;268(27):20343-51) and Arkovitz (Journal of Surgical Research, (1997 Feb 1) 67 (2) 193 8).

Claims 1–10 and 89–96 are directed to or encompass a method of treat comprising improving and/or normalizing lung function in a patient in need of such treatment, a method of treat comprising improving and/or normalizing pulmonary compliance in a patient in need of such treatment, and a method of treatment comprising improving blood oxygenation and/or normalizing blood pH in a patient in need of such treatment. According to the present specification, patients with RDS are patients in need of improving and/or normalizing lung

function and pulmonary compliance and in need of improving blood oxygenation and/or normalizing blood pH (page 6, lines 4-23). The examiner uses applicants' specification as a dictionary for a definition of the term "patient in need of said treatment."

According to Arkovitz, in the pediatric population, oxygen is administered to neonates as part of the treatment of newborn respiratory distress syndrome. Prolonged exposure to oxygen leads to the development of chronic lung disease or death. In premature infants this chronic lung injury is called bronchopulmonary dysplasia (BPD). Infants with BPD have persistent pulmonary dysfunction and frequent hospitalizations and often develop secondary cardiac disease. See page 193, paragraph bridging left and right columns. Hyperoxia has been shown to decrease pulmonary compliance (page 193, right column, last full paragraph).

Claims 193–198 and 200 of copending Application No. 11/189,229 are directed to a method of decreasing vascular permeability in a patient. According to the specification of copending Application No. 11/189,229, pro-inflammatory treatments to the lungs, such as 100% oxygen exposure, generally increase vascular permeability, resulting in excess protein in BAL fluids (page 23, lines 9-10). The examiner uses the specification as a dictionary for a definition of patients for which decreasing vascular permeability may be indicated.

Therefore, a method of improving and/or normalizing lung function, blood pH or blood oxygenation encompasses or overlaps a method decreasing vascular permeability because each treatment method encompasses the treatment of same patient population with overlapping doses of the same compound.

According to Mantile, Ala-Ala was added to the NH_2 terminus as a consequence of plasmid construction (page 20348, Table I), which resulted in a higher efficiency of expression (page 20346, paragraph bridging left and right columns).

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Guy (Biochem Biophys Res Commun. 1992 Dec 15;189(2):662-9) discloses that exogenous surfactant therapy improves in infants with RDS. Guy's results imply that UG may protect both endogenous and exogenous surfactant from PLA_2 hydrolysis. Moreover, the antiinflammatory properties of UG may prevent the development of chronic inflammatory lung disease, a frequent complication of RDS. See the Abstract. Positive pressure ventilation used during treatment of RDS releases eicosanoids. Many of these eicosanoids can cause inflammation, a frequent finding in the lungs of preterm infants with RDS (paragraph bridging pages 662-663). The levels of UG and proinflammatory eicosanoids are inversely related in the fetal lung (page 663, full paragraph 1). There is a necessity for further investigation using an animal model of RDS to determine whether recombinant human UG-like protein administered in conjunction with surfactant further improves outcome in infants with RDS and decreases the incidence of CLD (page 667, last paragraph).

According to the Federal Register (August 16, 1994) Dr. Anil Mukherjee, an investigator in the National Institute of Child Health and Human Development (NICHD), is interested in

determining whether endotracheal administration of aerosolized recombinant human uteroglobin (UG) or antiflammins derived from the sequence of this protein in combination with surfactant prevents the development of the inflammatory lung disease bronchopulmonary dysplasia (BPD) in (a) non-human primate models of neonatal respiratory distress syndrome (RDS) and (b) human neonatal RDS in a multi-center study, provided the non-human primate study results show no toxicity and considerable improvement as a result of combination therapy with surfactant plus human uteroglobin.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, MANJUNATH RAO, CAN BE REACHED AT (571)272-0939.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID S ROMEO/
PRIMARY EXAMINER, ART UNIT 1647

DSR
JUNE 7, 2008